was added DIPEA (5.33 mL, 30.6 mmol) and DMSO (7.24 mL, 102 mmol) and stirred at rt for 5 min. The mixture was cooled to −40° C. and to this was added 5-heyn-1-ol (1.00 g, 10.2 mmol). The reaction was stirred for 2 h at −40° C., followed by 1 h at −10° C. then 1 h at rt. Upon completion, the reaction was acidified to pH 3 with 1M HCl and diluted with CH_2Cl_2 (10 mL). The layers were separated and the aqueous phase was extracted with further CH_2Cl_2 (2×20 mL). The combined organic fractions were washed with brine (2×50 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude oil was immediately redissolved in MeOH (10 mL). To this solution was added ethyl 4-aminobutyrate hydrochloride (2.05 g, 12.2 mmol) and triethylamine (2.84 mL, 20.4 mmol) and the mixture stirred at room temperature for 16 h. The reaction mixture was then cooled to 0° C. and to this was added sodium borohydride (578 mg, 15.3 mmol). The reaction was warmed to rt and stirred for 2 h. Upon completion, the reaction mixture was concentrated in vacuo, redissolved in CH_2Cl_2 and quenched with H_2O. The layers were separated and the aqueous phase extracted with further CH_2Cl_2 (3×15 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified by FCC (0-7.5% MeOH/CH_2Cl_2) to yield ethyl 4-(hex-5-yn-1-ylamino)butanoate (175 mg, 0.828 mmol, 8%) as a clear oil.

b) Ethyl 4-((4,6-dichloropyrimidin-2-yl)(hex-5-yn-1-yl)amino)butanoate (42)

[0357] A solution of 2,4,6-trichloropyrimidine (68.0 μL, 0.592 mmol), ethyl 4-(hex-5-yn-1-ylamino)butanoate 41 (150 mg, 0.710 mmol) and triethylamine (165 μL, 1.18 mmol) in acetone was stirred at 0° C. for 2.5 h. Upon completion, the reaction was concentrated in vacuo and the residue redissolved in H_2O (10 mL), saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (20 mL). The layers were separated and the aqueous phase was extracted with further CH_2Cl_2 (3×20 mL). The combined organic fractions were dried ($MgSO_4$), concentrated in vacuo and the crude residue purified by FCC (3-20% EtOAc/PE) to yield ethyl 4-((4,6-dichloropyrimidin-2-yl)(hex-5-yn-1-yl)amino)butanoate (32.0 mg, 89.0 μmol, 15%) as a white solid.

c) Ethyl 4-((4,6-divinylpyrimidin-2-yl)(hex-5-yn-1-yl)amino)butanoate (43)

[0358] A solution of ethyl 4-((4,6-dichloropyrimidin-2-yl)(hex-5-yn-1-yl)amino)butanoate 42 (23.0 mg, 64.2 μmol), potassium vinyltrifluoroborate (43.0 mg, 321 μmol), $Pd(dppf)Cl_2.CH_2Cl_2$ (8.00 mg, 9.63 μmol) and potassium carbonate (53.0 mg, 385 μmol) in THF/H_2O (10:1, 1.1 mL) was heated to 70° C. for 20 h. Upon completion, the reaction mixture was filtered through Celite® and the solvent removed in vacuo. The resulting residue was purified by flash column chromatography (FCC, 5% EtOAc/PE) to yield ethyl 4-((4,6-divinylpyrimidin-2-yl)(hex-5-yn-1-yl)amino)butanoate (11.5 mg, 33.7 μmol, 53%) as a pale yellow oil.

d) 4-((4,6-divinylpyrimidin-2-yl)(hex-5-yn-1-yl)amino)butanoic acid (44)

[0359] A solution of ethyl 4-((4,6-divinylpyrimidin-2-yl)(hex-5-yn-1-yl)amino)butanoate 43 (8.00 mg, 23.4 μmol) and $LiOH.H_2O$ (4.00 mg, 93.8 μmol) in THF/H_2O (0.5 mL, 1:1) was stirred at rt for 21 h. Upon completion, the reaction was diluted with H_2O (10 mL) and washed with Et_2O (10 mL). The aqueous phase was neutralised with 1M HCl and extracted with CH_2Cl_2 (4×20 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo to yield 4-((4,6-divinylpyrimidin-2-yl)(hex-5-yn-1-yl)amino)butanoic acid (6.30 mg, 20.1 μmol, 86%) as a pale yellow oil.

References

Reference	DOI
Badescu 2014: G. Badescu, P. Bryant, M. Bird, K. Henseleit, J. Swierkosz, V. Parekh, R. Tommasi, E. Pawlisz, K. Jurlewicz, M. Farys, et al., *Bioconjug. Chem.* 2014, 25, 1124-36	10.1021/bc500148x
Beck 2017: A. Beck, L. Goetsch, C. Dumontet, N. Corvaïa, *Nat. Rev. Drug Discov.* 2017, 16, 315-337	10.1038/nrd.2016.268
Behrens 2015: C. R. Behrens, E. H. Ha, L. L. Chinn, S. Bowers, G. Probst, M. Fitch-Bruhns, J. Monteon, A. Valdiosera, A. Bermudez, S. Liao-Chan, et al., *Mol. Pharm.* 2015, 12, 3986-3998	10.1021/acs.molpharmaceut.5b00432
Chudasma 2011: V. Chudasama, M. E. B. Smith, F. F. Schumacher, D. Papaioannou, G. Waksman, J. R. Baker, S. Caddick, *Chem. Commun.* 2011, 47, 8781	10.1039/c1cc12807h
Chudasma 2016: V. Chudasama, A. Maruani, S. Caddick, *Nat. Chem.* 2016,8, 114-119	10.1038/nchem.2415
Junutula 2008: J. R. Junutula, H. Raab, S. Clark, S. Bhakta, D. D. Leipold, S. Weir, Y. Chen, M. Simpson, S. P. Tsai, M. S. Dennis, et al., *Nat. Biotechnol.* 2008, 26, 925-32	10.1038/nbt.1480
Lyon 2014: R. P. Lyon, J. R. Setter, T. D. Bovee, S. O. Doronina, J. H. Hunter, M. E. Anderson, C. L. Balasubramanian, S. M. Duniho, C. I. Leiske, F. Li, et al., *Nat. Biotechnol.* 2014, 32, 1059-62	10.1038/nbt.2968
Maruani 2015: A. Maruani, M. E. B. Smith, E. Miranda, K. A. Chester, V. Chudasama, S. Caddick, *Nat. Commun.* 2015, 6, 6645	10.1038/ncomms7645
Nunes 2015: J. P. M. Nunes, M. Morais, V. Vassileva, E. Robinson, V. S. Rajkumar, M. E. B. Smith, R. B. Pedley, S. Caddick, J. R. Baker, V. Chudasama, *Chem. Commun.* 2015, 51, 10624-10627	10.1039/c5cc03557k